Does hydrochlorothiazide increase the incidence of skin, lip and oral cancer in a UK population?

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A Commentary on

Morales D R, Pacurariu A, Slattery J, Kurz X

Association between hydrochlorothiazide exposure and different incident skin, lip and oral cavity cancers: A series of population-based nested case-control studies. *Br J Clin Pharmacol* 2020; **86:** 1336–1345.

Practice points

- Inclusion of precautions in product information, due to the plausibility that higher cumulative doses of HCTZ may increase the risk of NMSC and lip cancer, which can also help to inform discussion of risk/benefit with patients.
- Ensure healthcare professionals are aware of the increased risk of NMSC and lip cancer associated with HCTZ use and encourage patients to use adequate sun protection and limit their exposure.
- Healthcare professionals should have a low threshold for referring lesions suspicious of SCC skin, BCC skin and lip cancer in patients with HCTZ exposure.

Abstract

Data sources Data was from The Health Improvement Network (THIN) database from January 1999 to May 2016.

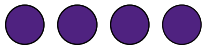
Study selection This was a series of population-based, case-control studies looking to evaluate the association between hydrochlorothiazide (HCTZ) exposure and skin, lip and oral cancer in the UK population.

Case/control selection Using the THIN database, patients with the following outcomes were grouped: squamous cell carcinoma (SCC) skin cancer; basal cell carcinoma (BCC) skin cancer; melanoma; lip cancer and oral cancer. Patients within the lip cancer and oral cancer groups were accepted with a history of non-melanoma skin cancer (NMSC). Patients in the SCC and BCC groups were not accepted with a history of cancer. Patients with a history of organ transplantation, human immunodeficiency virus (HIV) or immunosuppressant drug use before the index date were not accepted, due to the risk of predisposition to cancer. Controls were randomly selected using incidence density sampling. Up to 100 controls were randomly selected, matched on sex, exact year of birth and calendar year of cohort entry for lip cancer. However, for the remaining outcomes, only 20 controls were matched as above. Adults with incident NMSC, melanoma, lip cancer and oral cancer were matched to controls. Incidence rate ratios (IRRs) for the aforementioned outcomes were calculated for every cumulative HCTZ exposure.

Data analysis Odds ratios were calculated using conditional logistic regression. Associations were presented using a two-year HCTZ exposure lag-time and a five-year HCTZ exposure lag-time. Associations were evaluated using sensitivity analysis, restricted to patients with at least ten years' follow-up. There was adjustment for smoking status and BMI. Published incidence rates were used to calculate the absolute risk estimate for SCC as the incidence of SCC in the cohort was less than expected. For high-dose cumulative HCTZ exposure, the number of patients needed to treat to cause one additional cancer (number needed to harm) per year overall was estimated using rate differences. Analysis was carried out using SAS Enterprise Guidev7.1 and STATAv15.

Results Relative incidence of SCC, BCC and lip cancer was significantly elevated with every use of HCTZ. Relative incidence of melanoma and oral cancer was not significantly elevated with HCTZ exposure. Smoking was inversely associated with BCC and melanoma risk, but significantly increased the risk of lip and oral cavity cancers. SCC risk was not strongly associated with smoking. Significantly reduced risk of SCC, BCC melanoma and oral cavity cancer was associated with a BMI ≥30 kg/m^2.

Conclusions The risk of NMSC and lip cancer in a UK population is increased with cumulative high-dose HCTZ exposure. It is therefore important for dentists to note as it may increase suspicion of lesions in patients taking these medications.

GRADE rating 

Commentary

Hydrochlorothiazide (HCTZ) can be used in the management of hypertension, congestive cardiac failure and oedema. HCTZ can cause photosensitivity and therefore increase UV light-induced DNA damage.[1] Following laboratory and epidemiologic evidence linking drug-induced photosensitivity to skin cancer, HCTZ was classified as possibly carcinogenic to humans by the International Agency for Research on Cancer (IARC) in 2013.[2]

Epidemiological studies from Denmark recently reported HCTZ use is strongly associated with an increased risk of lip cancer and non-melanoma skin cancer (NMSC), especially squamous cell carcinoma (SCC).[3,4,5] Previous Danish studies have produced conflicting reports over association of HCTZ use and risk of melanoma development.[6,7]

This study aimed to evaluate whether similar associations between HCTZ exposure and skin cancer are observed in a different population and to assess the impact of adjusting for confounding factors, such as smoking and BMI, to allow for calculation of absolute risk.

The authors used data from The Health Improvement Network (THIN). This is anonymised, longitudinal patient

data from primary care records which is representative of the UK population in terms of age, sex, deprivation status and geographical distribution.[8] This large, national source of data allows the risk to be examined in patients with different UV skin susceptibility and phenotype. However, it does not have the longitudinal follow-up that Danish registries had, therefore limiting the exploration of association between HCTZ and skin cancer outcome.

Outcomes evaluated were: SCC skin cancer; BCC skin cancer; melanoma; lip cancer; and oral cancer. Oral cancer was used as a negative control, as cancers of the oral cavity and pharynx share similar risk factors for cancer development but are not exposed to significant UV light. This was useful in testing for unmeasured confounding factors. No elevated association between HCTZ exposure and oral cancer development was observed, which suggests that unmeasured confounding by risk factors common to skin/lip cancer and oral cancer does not explain the observed associations.

Results showed a statistically significant elevated relative incidence of skin SCC, skin BCC and lip cancer with HCTZ exposure, but this varied according to cumulative dose and the definition of the exposure lag-time period used. A small, elevated risk of melanoma was unable to be excluded, although no significantly increased risk was observed. P values were not provided; however, statistical significance was inferred from the 95% confidence intervals. Absolute risk from cumulative use of HCTZ was greatest in those aged 60 or greater.

These results, from a different population and data source than the Danish studies, showed similar association between HCTZ and skin cancer. They found a fourfold increased risk of SCC and a 1.3-fold increased risk of BCC with ≥50,000 mg cumulative HCTZ exposure. The study was unable to evaluate the association with melanoma and HCTZ; however, previous Danish studies have reported contrasting results, with one reporting no significant association and one reporting a statistically significant increased risk.[3,4,5,6,7]

Limitations of this study include absence of data regarding sun exposure, skin pigmentation and family history of melanoma. These were unreported cofounders which may have influenced the results.

Strengths of the study included adjustment for age, sex, drugs with suggested photosensitising properties or antineoplastic effects, history of alcohol abuse, diabetes, COPD and the use of Charlson Comorbidity Index score. This, coupled with adjustment for smoking and BMI, allowed for calculation of absolute risk.

In conclusion, HCTZ use is associated with an increased risk of skin SCC, skin BCC and lip cancer, with a greater risk in those aged 60 and greater.

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